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ARTICLE

Copanlisib population pharmacokinetics from phase I–III studies and exposure–response relationships in combination with rituximab

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Abstract

Copanlisib dose selection was established under the maximum tolerated dose paradigm, and no dedicated dose-finding studies have investigated copanlisib dose selection when used in combination with rituximab. In CHRONOS-3, copanlisib plus rituximab demonstrated significantly improved progression-free survival versus placebo plus rituximab in patients with relapsed indolent non-Hodgkin lymphoma (iNHL). We conducted a comprehensive investigation of copanlisib population pharmacokinetics (PopPK) from a pooled analysis of 712 patients across nine copanlisib phase I–III studies and exposure–response (ER) relationships for efficacy and safety from the 1-year follow-up of CHRONOS-3. PopPK analyses examined the impact of demographic, laboratory, and comedication covariates on copanlisib between-patient PK variability. Individual static and time-varying exposure estimates were derived to investigate exposure–efficacy and exposure–safety relationships. Multivariate Cox proportional hazards and logistic regression analyses examined ER relationships with consideration of predefined potentially prognostic demographic-, laboratory-, and/or disease-related baseline covariates. Copanlisib PK were best described by a three-compartment model with first-order elimination. Individual identified covariates had modest effects on copanlisib PK and were generally in line with known copanlisib disposition properties. In CHRONOS-3, ER analyses showed a significant relationship between time-varying exposure estimates and progression-free survival, and no significant exposure–safety relationships. Thus, lower copanlisib doses may result in reduced efficacy but not necessarily improved safety or tolerability. These outcomes substantiate the current intermittent dosing regimen of copanlisib 60 mg

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Trial registration ID: NCT02367040.

on days 1, 8, and 15 of a 28-day cycle and support the observed clinical results of copanlisib in combination with rituximab in the iNHL population.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

Copanlisib monotherapy is approved for relapsed follicular lymphoma and demonstrated superior progression-free survival (PFS) in combination with rituximab versus placebo in the phase III CHRONOS-3 study with an intermittent flat dosing regimen.

WHAT QUESTION DID THIS STUDY ADDRESS?

We investigated population pharmacokinetic (PK) and exposure–response (ER) relationships for copanlisib efficacy and safety from a pooled analysis, based on 1-year follow-up data from CHRONOS-3.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

These results comprehensively characterized copanlisib PK, identified and quantified sources of between-patient variability, and illustrated limited exposure variations in patient subgroups. Multivariate ER analyses demonstrated a positive exposure–PFS relationship (greater copanlisib exposure was associated with prolonged PFS) and showed no exposure–safety relationships following administration of the copanlisib 60 mg intermittent dosing regimen with rituximab in the indolent non-Hodgkin lymphoma (iNHL) population.

HOW MIGHT THIS CHANGE DRUG DISCOVERY, DEVELOPMENT, AND/OR THERAPEUTICS?

Administration of copanlisib 60 mg on days 1, 8, and 15 of a 28-day cycle in combination with rituximab in the relapsed iNHL population was substantiated and supports an overall positive risk/benefit assessment of copanlisib.

INTRODUCTION

Copanlisib (Bayer AG) is a novel, intravenous, potent, and highly selective pan-class I phosphatidylinositol 3-kinase (PI3K) inhibitor with predominant activity against PI3K-α and -δ isoforms (half-maximal inhibitory concentration [IC_{50}] values of 0.5 and 0.7 nmol/L, respectively).[1] Robust antitumor and pro-apoptotic activity was observed in various tumor cell lines and xenograft models,[2] with nonclinical studies supporting an intermittent dosing schedule for copanlisib.[2,3] Initial copanlisib concentrations in plasma and tumor suppressed tumor growth, whereas the intervals with plasma copanlisib concentrations below the IC_{50}/90% inhibitory concentration (IC_{90}) provided time for healthy organs and tissues to recover.[3,4] Consequently, the intermittent dosing schedule was proposed to be important for achieving efficacy while maintaining tolerability.

Based on an initial dose-finding assessment from the phase I first-in-human clinical study (NCT00962611), the maximum tolerated dose (MTD) of copanlisib was determined to be 0.8 mg/kg administered intravenously in an intermittent dosing schedule on days 1, 8, and 15 of a 28-day cycle (3 weeks on/1 week off).[5] Copanlisib showed dose-proportional pharmacokinetics (PK) following intravenous infusion up to and including the MTD.[5] At the MTD, maximal concentrations exceeded the in vitro cellular IC_{90} for PI3K isoforms and thereafter declined with a half-life of around 38 h; therefore, concentrations at 1 week after dosing fell below the in vitro IC_{90} target, reflecting transient target engagement.[5] Initial modeling and simulation analyses supported that a fixed dose of copanlisib 60 mg on the intermittent schedule is likely to achieve a risk/benefit ratio similar to that of 0.8 mg/kg weight-based dosing[6]; thus, this fixed dose has been used in all clinical studies.

The initial phase II CHRONOS-1 study (NCT01660451) established the risk/benefit profile of copanlisib monotherapy dosed at 60 mg as a 1-h intravenous infusion on days 1, 8, and 15 of a 28-day cycle in patients with relapsed or refractory indolent B-cell lymphoma who had previously received at least two therapies, demonstrating an objective response rate (ORR) of 59% and a manageable safety profile.[7] Based on these results, copanlisib received approval as monotherapy for relapsed follicular lymphoma in adult patients who have received at least two systemic therapies.[8–10] In the

randomized, double-blind, phase III CHRONOS-3 trial (NCT02367040), copanlisib at a fixed intermittent dose of 60 mg plus standard rituximab demonstrated superior progression-free survival (PFS) over placebo plus rituximab in patients with relapsed indolent non-Hodgkin lymphoma (iNHL; hazard ratio: 0.52; 95% confidence interval [CI]: 0.39, 0.69); this benefit was confirmed in the overall population and in the subset of patients with follicular lymphoma in an updated 1-year follow-up analysis.[11–13] Generally acceptable tolerability of the combination was demonstrated based on safety assessments reported in CHRONOS-3; however, some form of dose interruption or delay was reported in 75.2% (231/307) of patients receiving copanlisib plus rituximab in CHRONOS-3.[11]

Copanlisib dose selection was established under the MTD paradigm, and no dedicated dose-finding studies have investigated copanlisib dose selection when used in combination with rituximab. To better understand and quantify sources of between-patient variability in copanlisib PK and to investigate copanlisib dose selection, we report the first comprehensive assessment of copanlisib population PK (PopPK) of phase I–III studies and exposure–response (ER) relationships in relapsed iNHL in combination with rituximab based on data from the 1-year follow-up analysis of CHRONOS-3.

METHODS

Compliance with ethics guidelines

All patients provided written, informed consent. The modeling and simulation activities were conducted in accordance with the recent US Food and Drug Administration guidance on PopPK[14] and reported in accordance with the respective European Medicines Agency guideline.[15]

Copanlisib PopPK modeling

A comprehensive PopPK model for copanlisib was developed using 5958 plasma concentrations from 712 patients across nine phase I–III studies (Table S1).[5,7,11,16–22] Copanlisib concentrations were analyzed in plasma samples using validated and cross-validated liquid chromatography/mass spectrometry assays with a lower limit of quantification of 2 ng/mL. Observations for 276 samples were below the lower limit of quantification and were incorporated into the model inference using the M3 method.[23] PK model building was conducted using nonlinear mixed-effects modeling with NONMEM software version 7.4.3 (ICON plc). One-, two-, and three-compartment structural models were investigated for their ability to describe copanlisib PK. Subsequently, demographic, laboratory, and comedication covariates were investigated for their influence on copanlisib between-patient PK variability using a full stepwise forward inclusion/backward elimination procedure (Table S2). During forward inclusion, a reduction in the objective function value (OFV) corresponding to $p<0.001$ (ΔOFV -10.828 for one estimated parameter) was required for significance, whereas in backward elimination the requirement was increased to $p<0.0001$ (ΔOFV $+15.137$ for one estimated parameter). The covariate influences were implemented in the PopPK model as follows:

Allometric scaling used for investigation of body weight:

$$P_i = \theta_{TV} \bullet \left(\frac{BW_i}{BW_{med}}\right)^{\theta_{cov}} \bullet \exp(\eta_i)$$

Continuous covariates:

$$P_{i,m}P_i = \theta_{TV} \bullet \exp\left(\theta_{cov} \bullet \left(COV_i - COV_{med}\right)\right) \bullet \exp(\eta_i)$$

Categorical covariates:

$$P_i = \theta_{TV} \bullet \left(1 + N1 \bullet \theta_{cov1} + N2 \bullet \theta_{cov2} + \ \ldots\right) \bullet \exp(\eta_i)$$

where P_i denotes the individual model parameter estimate, θ_{TV} the estimated typical parameter value, BW_i the individual's body weight, and BW_{med} the population median body weight; COV_i and COV_{med} are the individual and population median covariate values, respectively; θ_{cov} is the estimated parameter for the covariate influence; $N1=N2=0$ is the most prevalent covariate category, $N1=1$ and $N2=0$ is the next most prevalent category, $N1=0$ and $N2=1$ is the next category, etc.

Model qualification for the final structural model and identified covariates was determined based on improvements in objective function criteria, lack of deviations in diagnostic plots, and through inspection of visual predictive checks (with time after dose as abscissa axis) derived from 1000 repeat simulations of the entire data set. A forest plot was generated to investigate how copanlisib exposure (area under the curve $[AUC][_{0-168}]_{nd}$, defined below) varies across patient subgroups.

Determination of copanlisib exposure metrics for investigation in the ER analysis

Numerical integration of the selected PopPK covariate model was used to predict individual copanlisib exposure variables for all copanlisib-treated patients included in the

ER analysis. Individual model parameters were used for all patients who contributed at least one PK observation to the model development. Population model parameters were used in the infrequent case (9.5%) where a patient did not contribute any PK observations to model development; in this case, variability in exposure came only from variability in individual covariate values.

Two types of copanlisib exposure variables were investigated: (1) one time-invariant (static) exposure variable defined as the individual PopPK model-predicted AUC from 0 to 168 h ($AUC_{[0–168]nd}$) after the third 60 mg nominal dose in a sequence of three doses of 60 mg each 1 week apart; and (2) three variations of time-varying exposure variables using PopPK model-predicted average concentration over 2, 4, and 8 weeks ($C_{avg,2wk}$, $C_{avg,4wk}$, and $C_{avg,8wk}$) as a moving average, based on each individual's actual dosing history – to robustly account for dose modifications, interruptions, and delays, for time-to-event analyses. Given the dynamic nature of the time-varying exposure variables, investigations into correlations between exposure variables were challenging, supporting the derivation and evaluation of all three time-varying exposure variables in the conducted ER analyses.

ER analyses

Exposure–efficacy analyses were undertaken to investigate the relationship between copanlisib exposure metrics and both PFS and ORR in CHRONOS-3. For all ER analyses, the data inclusion period was from randomization until 14 days after the last dose of copanlisib or placebo; follow-up data were not included. The exposure–PFS relationship was explored graphically using a Kaplan–Meier analysis stratified by $AUC_{(0–168)nd}$ and using a multivariate Cox proportional hazards (CPH) analysis as per below:

$$\lambda_i(t) = \lambda_0(t) \bullet \exp\left(\beta_1 \bullet X(t)_i + \boldsymbol{\beta}^T \bullet \boldsymbol{Z_i}\right)$$

where $\lambda_i(t)$ is the hazard function for patient i; t is the time in days; $\lambda_0(t)$ is the baseline hazard; β_1 is a numerical coefficient; $X(t)_i$ is the static or time-dependent exposure variable for patient i; $\boldsymbol{\beta}^T$ is a vector of numerical coefficients; and $\boldsymbol{Z_i}$ is a vector of significant baseline covariates for patient i.

The analysis first assessed the simultaneous inclusion of all predefined baseline covariates (treatment arm, demographic- and disease-related baseline factors as dichotomous values), and a series of backward elimination steps removed one by one the covariates with the weakest influence until only significant covariates ($p < 0.01$) remained in the model (Table S3). This model was called the reduced baseline covariate model (RBCM). Individual copanlisib exposure metrics were tested in the RBCM only when the RBCM included the treatment arm as a covariate – that is, in competition with significant covariates remaining in the RBCM. If copanlisib exposure variables (static and/or time-varying) were a significant predictor ($p < 0.01$), exposure was deemed to influence PFS beyond the effect of treatment and all other tested covariates. The assumption of proportional hazards was evaluated through evaluation of Schoenfeld residuals.[24] Forest plots were generated to provide the hazard ratios and 95% CIs of all significant baseline covariates and exposure variables. Exposure–ORR relationship was explored through a multivariate logistic regression analysis as per below:

$$logit\left(p_i(\boldsymbol{x})\right) = \log\left(\frac{p_i(\boldsymbol{x})}{1 - p_i(\boldsymbol{x})}\right) = \beta_0 + \boldsymbol{\beta}^T\boldsymbol{x}$$

where $\boldsymbol{x} = (x_1, \ldots, x_n)$ is a vector of predictors; $\boldsymbol{\beta} = (\beta_1, \ldots, \beta_n)$ is a vector of coefficients; β_0 is the intercept; $p_i(\boldsymbol{x})$ is the probability of event i as a function of predictors $\boldsymbol{x}$; and $logit\left(p_i(\boldsymbol{x})\right)$ is the logistic function.

The multivariate logistic regression was conducted in a similar procedure to the CPH analysis. Thereafter, copanlisib static exposure ($AUC_{[0–168]nd}$) was tested if the RBCM included the treatment arm. Results were tabulated and additionally included univariate logistic regression plots of copanlisib exposure ($AUC_{[0–168]nd}$) versus ORR.

Exposure–safety analyses were investigated in CHRONOS-3. Univariate logistic regression analyses initially explored the relationship between copanlisib exposure ($AUC_{[0–168]nd}$) and frequency of serious adverse events (SAEs) and of treatment-emergent adverse events (TEAEs) that were grade 3 or worse. Multivariate CPH analysis investigated exposure–safety relationships for time to SAEs and time to TEAEs that were grade 3 or worse. Only the first occurrence of each event was counted as a safety event. If a patient did not experience the event of interest, they were right-censored 14 days after the last dose of copanlisib or placebo or at the time of primary completion, whichever occurred sooner. Multivariate logistic regression using a similar approach to the exposure–ORR analysis was used to determine frequency of other investigated safety events, including hyperglycemia, hypertension, diarrhea, nausea, fatigue, lung infections (including pneumonitis), and neutropenia of any grade. Finally, an exploratory evaluation of the impact of copanlisib exposure ($AUC_{[0–168]nd}$) on copanlisib relative dose intensity (RDI) was evaluated graphically to assess whether higher copanlisib exposures were associated with reduced RDI. The RDI was defined via the following equation:

$$\text{RDI} = 100 \bullet (\text{Total mg received since randomization}) / (\text{Cumulative planned mg given nominal dosing})$$

Exposure simulations were accomplished in R version 3.6.1 (The R Foundation)[25] using the "RxODE" library.[26] The ER analyses were conducted using R with the "survival"[27] and "survminer"[28] libraries.

RESULTS

For the 712 patients across nine studies in the PopPK analysis, median age was 63 years (range: 20–91) and median body weight was 70.1 kg (range: 41.1–165); 52.4% of patients were female (Table 1).

PopPK meta-analyses

Copanlisib PK were best described by a linear three-compartment model with first-order elimination from the central compartment following intravenous infusion (Figure S1). All model parameters were estimated with acceptable standard errors (relative standard error <50%) and shrinkage (<30%; Table 2). Copanlisib PK were dose-proportional and time-independent, with no accumulation following the approved copanlisib dosing regimen of 60 mg administered on days 1, 8, and 15 of a 28-day cycle. The full stepwise forward inclusion/backward elimination procedure identified a PopPK covariate model which included eight significant covariates, and the parameter estimates encoded the following mean influences of covariates on the clearance (CL) and volume of distribution (V1) model parameters (listed in decreasing importance according to changes in OFV): (1) comedication with rifampin (a strong cytochrome P450 3A [CYP3A] inducer) increased CL by 191%; (2) comedication with itraconazole (a strong CYP3A inhibitor) decreased CL by 36.1%; (3) patients in CHRONOS-3 had 18.4% lower CL than patients in other studies; (4) females had 42.9% lower V1 than males; (5) females had 16.7% lower CL than males; (6) patients with mild or worse hepatic impairment had 19.2% lower CL than individuals with normal hepatic function; (7) comedication with rifampin increased V1 by 108%; and (8) patients from Japan had 20.4% lower CL than patients from other regions.

Adequacy of the final PopPK model in describing both the central tendency and the variability of copanlisib PK was confirmed by generating prediction-corrected visual predictive checks (Figure 1) and goodness-of-fit plots (Figure S2). Both visual predictive checks and goodness-of-fit plots demonstrated that the model describes the central tendency and variability of the observed PK data without any significant or consistent discrepancy or bias for the entire dataset and in CHRONOS-3.

Copanlisib exposure in CHRONOS-3

A forest plot with average variation in copanlisib exposure ($AUC_{[0–168]nd}$) by patient subgroup in CHRONOS-3 showed that the only comparison where the 90% CI of the geometric mean exposure ratio lay above 1.25 or below 0.8 was for patients living in Japan compared with Europe, where the geometric mean exposure ratio (1.34) and 90% CI (1.27, 1.43) were above 1.25 (Figure 2). The other covariates or subpopulations defined by sex, age, body weight, renal function, and geographic region showed exposure variations not exceeding traditional bioequivalence ranges (80–125%); thus, no covariate showed exposure differences greater than around 35%.

ER analyses

Out of 458 treated patients in CHRONOS-3, 447 were included in ER evaluations of PFS, ORR, and safety events. Of the 11 patients who were not included in the analysis, eight withdrew consent for data collection and three were randomized but never dosed.

Exposure–efficacy

Overall, 179 PFS events (40% incidence) occurred in CHRONOS-3, with 89 (29.5% incidence) in the copanlisib arm and 90 (62% incidence) in the placebo arm. An exploratory graphical evaluation by Kaplan–Meier analysis suggested a positive exposure–PFS relationship (Figure 3a). In the subsequent multivariate CPH analysis, the initial covariate search for PFS in all patients resulted in the following covariates included in the model: patients living in Japan; rituximab exposure; and treatment arm (Figure 3b). Testing copanlisib exposure variables on the RBCM for PFS in copanlisib-treated patients only demonstrated a statistically significant, positive ER relationship for PFS for all three time-varying copanlisib exposure estimates ($C_{avg,2wk}$: $p = 0.002$; $C_{avg,4wk}$: $p = 0.004$; $C_{avg,8wk}$: $p = 0.002$), along with a borderline significant ($p = 0.023$) relationship for copanlisib exposure expressed as time-invariant $AUC_{(0–168)nd}$ (Figure 3b), indicating that higher exposure in copanlisib-treated patients was associated with prolonged PFS. The assumption of proportional hazards was confirmed based on no observed trend in the Schoenfeld residuals ($p > 0.05$).

In CHRONOS-3, the number of overall ORR events was 297 (66.4% incidence), with 226 (74.8% incidence) in the copanlisib arm and 71 (49% incidence) in the placebo arm. An exploratory univariate logistic regression revealed no significant exposure–ORR relationship in CHRONOS-3

TABLE 1 Distribution of baseline covariates investigated in the PopPK and exposure–response analyses.

	Study 12871[a,5]	Study 15205[b,22]	Study 16270[c,17]	Study 16349 (Part A)[d,7,21]	Study 16349 (Part B)[d,7,21]	Study 16790[e,18]	Study 16866[f,16]	Study 17067[g,11]	Study 17792[h,19]	Study 18041[i,20]	Pooled PopPK analyses	Study 17067[j,11]
N	56	10	51	55	122	62	12	289	25	30	712	447
Age (years), median (range)	65 (33–86)	59.5 (51–65)	61 (20–81)	68 (22–90)	62 (25–82)	61.5 (38–80)	41.5 (30–64)	63 (28–91)	67 (39–75)	61.5 (31–78)	63 (20–91)	–
Sex, *n* (%)												
Male	20 (35.7)	4 (40.0)	20 (39.2)	25 (45.5)	63 (51.6)	21 (33.9)	7 (58.3)	145 (50.2)	13 (52.0)	21 (70.0)	339 (47.6)	234 (52.3)
Female	36 (64.3)	6 (60.0)	31 (60.8)	30 (54.5)	59 (48.4)	41 (66.1)	5 (41.7)	144 (49.8)	12 (48.0)	9 (30.0)	373 (52.4)	213 (47.7)
Body weight (kg), median (range)	72.6 (43.6–125.4)	57.0 (41.1–74.8)	72 (46.7–165)	69.5 (46.2–120)	73 (49–128)	67.4 (48.8–118)	73 (42.5–106)	69.5 (42.5–138)	58.6 (44.4–83.2)	81.4 (57.6–109.3)	70.0 (41.1–165)	–
Serum albumin (g/dL), median (range)	3.5 (1.6–4.8)	3.9 (3.5–4.6)	3.8 (2.8–4.5)	4.1 (2.8–6.5)	4.12 (2.5–5.2)	3.9 (2.4–5.87)	4.08 (3.0–4.5)	4.4 (2.8–5.2)	4.1 (1.9–4.7)	3.9 (2.2–4.8)	4.14 (1.6–6.5)	–
EGFR (mL/min), median (range)	82.37 (25.45–133.14)	80.73 (54.01–106.89)	95.17 (47.77–135.86)	77.62 (28.13–146.32)	90.57 (36.16–152.38)	84.44 (39.95–132.36)	114.40 (69.91–155.91)	87.97 (29.68–145.07)	81.27 (44.93–123.14)	87.37 (13.64–152.46)	87.9 (13.64–155.91)	–
Country/geographic region, *n* (%)												
North America	56 (100)	0	51 (100)	5 (9.1)	21 (17.2)	0	0	14 (4.8)	0	0	147 (20.6)	22 (4.9)
Europe	0	0	0	50 (90.9)	84 (68.9)	62 (100)	0	125 (43.3)	0	30 (100)	351 (49.3)	196 (43.8)
China	0	0	0	0	0	0	12 (100)	58 (20.1)	0	0	70 (9.8)	80 (17.9)
Japan	0	10 (100)	0	0	0	0	0	26 (9.0)	25 (100)	0	61 (8.6)	35 (7.8)
Asia (other)	0	0	0	0	8 (6.6)	0	0	20 (6.9)	0	0	28 (3.9)	53 (11.9)
Others	0	0	0	0	9 (7.4)	0	0	46 (15.9)	0	0	55 (7.7)	61 (13.6)
Renal function, *n* (%)												
Normal (NCI = 1)	21 (37.5)	4 (40.0)	30 (58.8)	19 (34.5)	63 (51.6)	26 (41.9)	9 (75.0)	137 (47.4)	10 (40.0)	14 (46.7)	333 (46.8)	166 (37.1)
Mild impairment (NCI = 2)	25 (44.6)	4 (40.0)	19 (37.3)	25 (45.5)	47 (38.5)	24 (38.7)	3 (25.0)	122 (42.2)	12 (48.0)	5 (16.7)	286 (40.2)	227 (50.8)
Moderate impairment (NCI = 3)	9 (16.1)	2 (20.0)	2 (3.9)	10 (18.2)	12 (9.8)	12 (19.4)	0	29 (10.0)	3 (12.0)	5 (16.7)	84 (11.8)	54 (12.1)
Severe impairment (NCI = 4)	1 (1.8)	0	0	1 (1.8)	0	0	0	1 (0.3)	0	6 (20.0)	9 (1.3)	0

TABLE 1 (Conitinued)

	Study 12871[a,5]	Study 15205[b,22]	Study 16270[c,17]	Study 16349 (Part A)[d,7,21]	Study 16349 (Part B)[d,7,21]	Study 16790[e,18]	Study 16866[f,16]	Study 17067[g,11]	Study 17792[h,19]	Study 18041[i,20]	Pooled PopPK analyses	Study 17067[j,11]
Hepatic function, *n* (%)												
Normal	42 (75.0)	5 (50.0)	42 (82.4)	48 (87.3)	111 (91.0)	51 (82.3)	11 (91.7)	246 (85.1)	22 (88.0)	21 (70.0)	599 (84.1)	377 (84.3)
Mild	14 (25.0)	5 (50.0)	9 (17.6)	7 (12.7)	11 (9.0)	11 (17.7)	1 (8.3)	42 (14.5)	3 (12.0)	3 (10.0)	106 (14.9)	68 (15.2)
Moderate	0	0	0	0	0	0	0	1 (0.3)	0	2 (6.7)	3 (0.4)	2 (0.4)
Severe	0	0	0	0	0	0	0	0	0	4 (13.3)	4 (0.6)	0
Additional baseline covariates for study 17067 exposure–response analysis for CHRONOS-3[8] (*N* = 447)												
Hypertension (first infusion), *n* (%)												
Yes				104 (23.3)								
No				343 (76.7)								
Hyperglycemia (first infusion), *n* (%)												
Yes				157 (35.1)								
No				290 (64.9)								
Neutrophil count, *n* (%)												
$<3500\,mm^3$				242 (54.1)								
$\geq 3500\,mm^3$				205 (45.9)								
Bulky disease, *n* (%)												
Yes				66 (14.8)								
No				381 (85.2)								
HbA_{1c}, *n* (%)												
<5.7%				263 (58.8)								
≥5.7%				184 (41.2)								
Recent chemotherapy, *n* (%)												
Yes				415 (92.8)								
No				32 (7.2)								
Recent PI3K inhibitor, *n* (%)												
Yes				7 (1.6)								
No				440 (98.4)								
Systemic cancer treatments, *n* (%)				2 (1–30)								
Recent rituximab treatment, *n* (%)												
Yes				221 (49.4)								
No				226 (50.6)								

TABLE 1 (Conitinued)

	Study 12871[a,5]	Study 15205[b,22]	Study 16270[c,17]	Study 16349 (Part A)[d,7,21]	Study 16349 (Part B)[d,7,21]	Study 16790[e,18]	Study 16866[f,16]	Study 17067[g,11]	Study 17792[h,19]	Study 18041[i,20]	Pooled PopPK analyses	Study 17067[j,11]
Rituximab dose (mg/L), *n*, median (range)												
Before third infusion				124.5 (0.25–450)								
After third infusion				324 (0.25–584)								
Before fourth infusion				174 (0.25–481)								
After fourth infusion				365 (0.25–849)								
Refractory disease, *n* (%)												
Yes				427 (95.5)								
No				20 (4.5)								
ECOG PS score, *n* (%)												
0				266 (59.5)								
1				181 (40.5)								
Histology, *n* (%)												
FL				265 (59.3)								
MZL				94 (21.0)								
SLL				50 (11.2)								
LPL/WM				38 (8.5)								

Abbreviations: aNHL, aggressive non-Hodgkin lymphoma; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, estimated glomerular filtration rate; FL, follicular lymphoma; HbA_{1c}, glycated hemoglobin; iNHL, indolent non-Hodgkin lymphoma; LPL/WM, lymphoplasmacytic lymphoma/Waldenström macroglobulinemia; MZL, marginal zone lymphoma; NCI, National Cancer Institute; PI3K, phosphatidylinositol 3-kinase; PopPK, population pharmacokinetics; SLL, small lymphocytic lymphoma.

[a]Study 12871: Phase I dose-escalation study of copanlisib in patients with solid tumors (NCT00962611).

[b]Study 15205: Phase I dose-escalation study of copanlisib in Japanese patients with solid tumors (NCT01404390).

[c]Study 16270: Phase I drug–drug interaction study of copanlisib in patients with advanced solid tumors (NCT02253420).

[d]Study 16349 (Parts A and B): Phase II study of copanlisib in patients with aNHL or iNHL (NCT01660451; CHRONOS-1).

[e]Study 16790: Phase I pharmacodynamic study of copanlisib in patients with iNHL or solid tumors (NCT03711058).

[f]Study 16866: Phase I study of copanlisib in Chinese patients with relapsed iNHL (NCT03498430).

[g]Study 17067: Phase III study evaluating the efficacy and safety of copanlisib in combination with rituximab in patients with relapsed iNHL (NCT02367040; CHRONOS-3).

[h]Study 17792: Phase Ib study in Japanese patients with iNHL relapsed after or refractory to standard therapy (NCT02342665).

[i]Study 18041: Phase I study of a single intravenous dose of copanlisib in patients with impaired hepatic or renal function compared with healthy participants (NCT03172884).

[j]Study 17067: Exposure–response analysis for CHRONOS-3.

TABLE 2 Parameter estimates from the copanlisib population pharmacokinetics covariate model.

Parameter	Unit	Estimate	RSE (%)[a]	LLCI[b]	ULCI[c]	Description
Fixed effects (THETA)						
CL_{pop}	L/h	22.2	3.18	20.8	23.5	Clearance for a patient with reference values of covariates[d]
$V1_{pop}$	L	92.1	7.47	78.6	106	Volume of distribution for compartment 1 for a patient with reference values of covariates[e]
Q2	L/h	79.3	1.58	76.8	81.7	Inter-compartment clearance for compartments 1 and 2
V2	L	508	2.54	483	534	Volume of distribution for compartment 2
Q3	L/h	7.34	6.96	6.34	8.34	Inter-compartment clearance for compartments 1 and 3
V3	L	522	4.26	478	565	Volume of distribution for compartment 3
Θ_{RIFCL}	–	1.91	3.56	1.78	2.04	Parameter describing influence of rifampin on clearance
Θ_{ITRACL}	–	−0.361	5.07	−0.397	−0.325	Parameter describing influence of itraconazole on clearance
$\Theta_{17067CL}$	–	−0.184	17.6	−0.248	−0.121	Parameter describing influence of study 17067 (CHRONOS-3) on clearance
Θ_{SEXV1}	–	−0.429	14.6	−0.552	−0.307	Parameter describing influence of sex on V1
Θ_{SEXCL}	–	−0.167	17.2	−0.224	−0.111	Parameter describing influence of sex on clearance
Θ_{NCICL}	–	−0.192	17.4	−0.257	−0.126	Parameter describing influence of NCI for any hepatic impairment category relative to normal hepatic function on clearance
Θ_{RIFV1}	–	1.08	39.0	0.256	1.91	Parameter describing influence of rifampin on V1
Θ_{JAPCL}	–	−0.204	29.3	−0.321	−0.0867	Parameter describing the influence of region = Japan on clearance
Random effects: inter-individual variability (OMEGA)						
CL (ω^2)	–	0.124	6.07	0.109	0.138	Variance of exponential inter-individual variability on CL_{pop}
CL (CV[f])	%	36.3		33.9	38.5	
CL (shrinkage)	%	22.5				
V1 (ω^2)	–	0.846	8.94	0.698	0.994	Variance of exponential inter-individual variability on $V1_{pop}$
V1 (CV[f])	%	115		100	130	
V1 (shrinkage)	%	27.3				
Residual error (SIGMA)						
σ^2	–	5.10	4.87	4.62	5.59	Variance of additive residual error for log-transformed observations during first 20 min of an infusion
CV[g]	%	1280		1000	1630	
σ^2	–	0.176	1.22	0.172	0.180	Variance of additive residual error for log-transformed observations in phase I and phase II studies after first 20 min of an infusion
CV[g]	%	43.9		43.3	44.5	
σ^2	–	0.632	2.44	0.601	0.662	Variance of additive residual error for log-transformed observations in phase III for study 17067 (CHRONOS-3) after first 20 min of an infusion
CV[g]	%	93.8		90.8	96.9	

Abbreviations: CL, clearance; CV, coefficient of variation; EXP, exponential; LLCI, lower limit of 95% confidence interval; NCI, National Cancer Institute; RSE, relative standard error; SE, standard error; SQRT, square root; ULCI, upper limit of 95% confidence interval.

[a]100·SE/estimate.

[b]Estimate −1.96·SE.

[c]Estimate +1.96·SE.

[d]Clearance of a typical patient with the following covariate values: male in a non-Japanese phase I or phase II study without co-administration of rifampin or itraconazole and NCI = 1 (normal liver function).

[e]Clearance of a typical patient with the following covariate values: male without co-administration of rifampin.

[f]CV calculated as 100·SQRT(EXP(ω^2) − 1). The confidence intervals of CV are derived through transformation of confidence intervals of ω^2.

[g]Both the observations and the model predictions were log-transformed, and an additive residual error model was used. This is equivalent to an exponential residual error model on untransformed data and the CV calculated as 100·SQRT(EXP(σ^2) − 1). The confidence intervals of CV are derived through transformation of confidence intervals of σ^2.

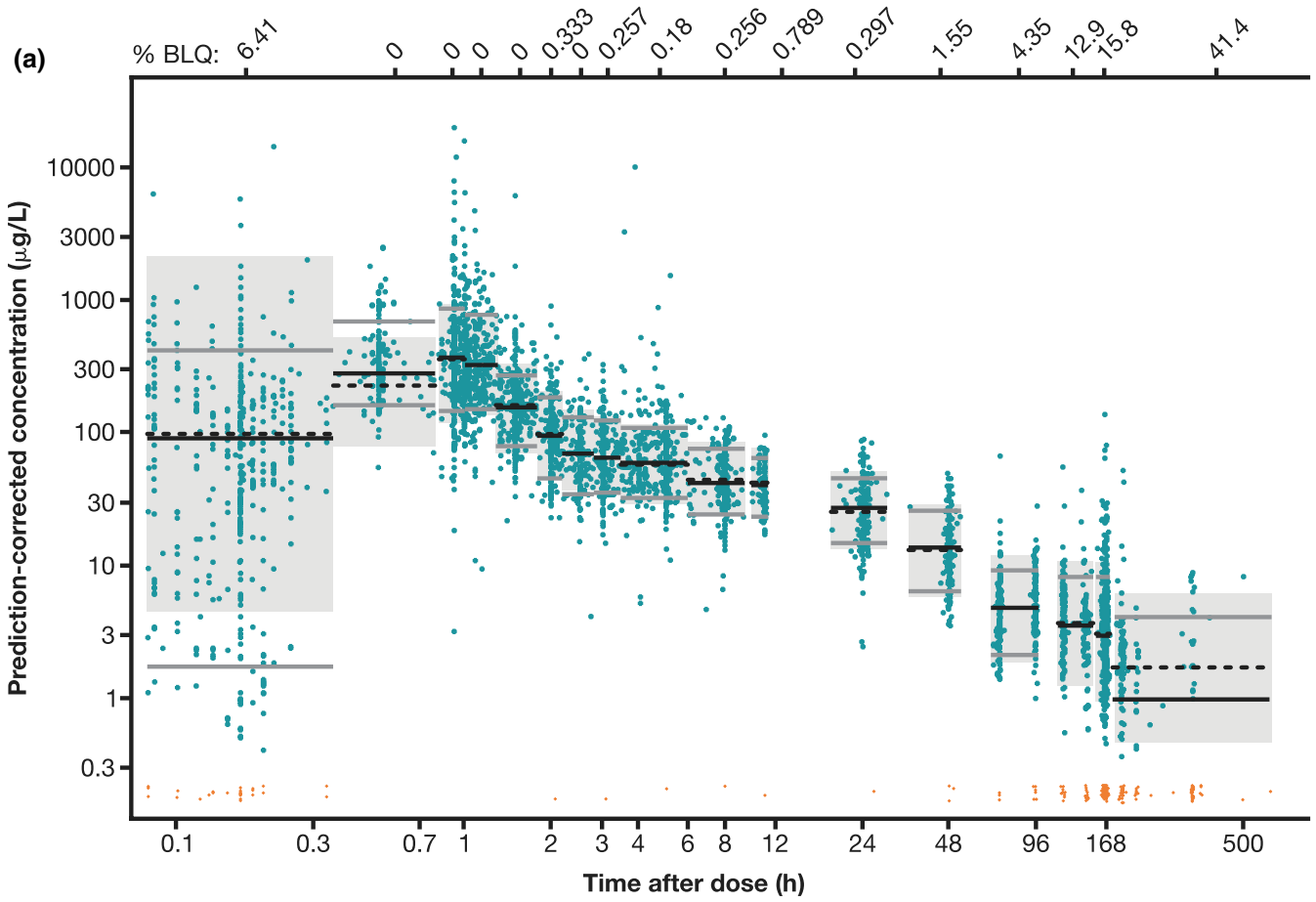


FIGURE 1 Prediction-corrected visual predictive checks of the final copanlisib population pharmacokinetics model in describing copanlisib pharmacokinetics from (a) all studies and (b) CHRONOS-3. All gray lines and shaded regions correspond to model simulations and all black lines correspond to observed data. Blue circles represent the prediction-corrected observations that are greater than the LLOQ; orange circles represent the observations less than the LLOQ jittered around 0.2 µg/L LLOQ on the *y*-axis; black horizontal lines represent the 50th percentiles of prediction-corrected observations in the bin; gray horizontal lines represent the 10th and 90th percentiles of prediction-corrected observations in the bin; black dotted horizontal lines represent the 50th percentile of prediction-corrected simulated values in the bin; gray shaded areas represent the range between the 10th and 90th percentiles of prediction-corrected simulated values in the bin; the numbers along the top of the plot represent the percentage of observations in the bin that are less than the LLOQ. BLQ, below the limit of quantification; LLOQ, lower limit of quantification. Panel (b) was previously presented in a poster at the Third AACR International Meeting, Advances in Malignant Lymphoma: Maximizing the Basic-Translational Interface for Clinical Application, June 23–26, 2022, Boston, MA, USA, and is reproduced with kind permission from Peter Morcos on behalf of all authors.

(Figure 4a). The multivariate analysis for CHRONOS-3 identified two covariates included in the RBCM: histology of follicular lymphoma and treatment arm. Results from multivariate analyses confirmed no significant ER relationship with frequency of ORR for copanlisib-treated patients ($p = 0.57$) following testing of the $AUC_{(0–168)nd}$ on the RBCM (Figure 4b). Thus, ORR was consistent throughout the exposure range in copanlisib-treated patients.

Exposure–safety

Overall, in CHRONOS-3, 164 SAEs were reported (36.7% incidence), with 135 (44.7% incidence) in the copanlisib arm and 29 (20% incidence) in the placebo arm. An exploratory univariate logistic regression revealed no significant exposure–SAE relationship (Figure 5a). Consistently, in the multivariate CPH analysis for time to SAE, the treatment arm was the only significant covariate included in the RBCM, and no significant ER relationship was identified between SAEs and the copanlisib exposure variables $AUC_{(0–168)nd}$ ($p = 0.93$), $C_{avg,2wk}$ ($p = 0.51$), $C_{avg,4wk}$ ($p = 0.81$), and $C_{avg,8wk}$ ($p = 0.72$; Figure 5b).

TEAEs of grade 3 or worse occurred in 357 out of 447 evaluable patients (79.9%) overall, with 275 (91% incidence) in the copanlisib arm and 82 (56.6% incidence) in the placebo arm. An exploratory univariate logistic regression revealed no significant relationship between

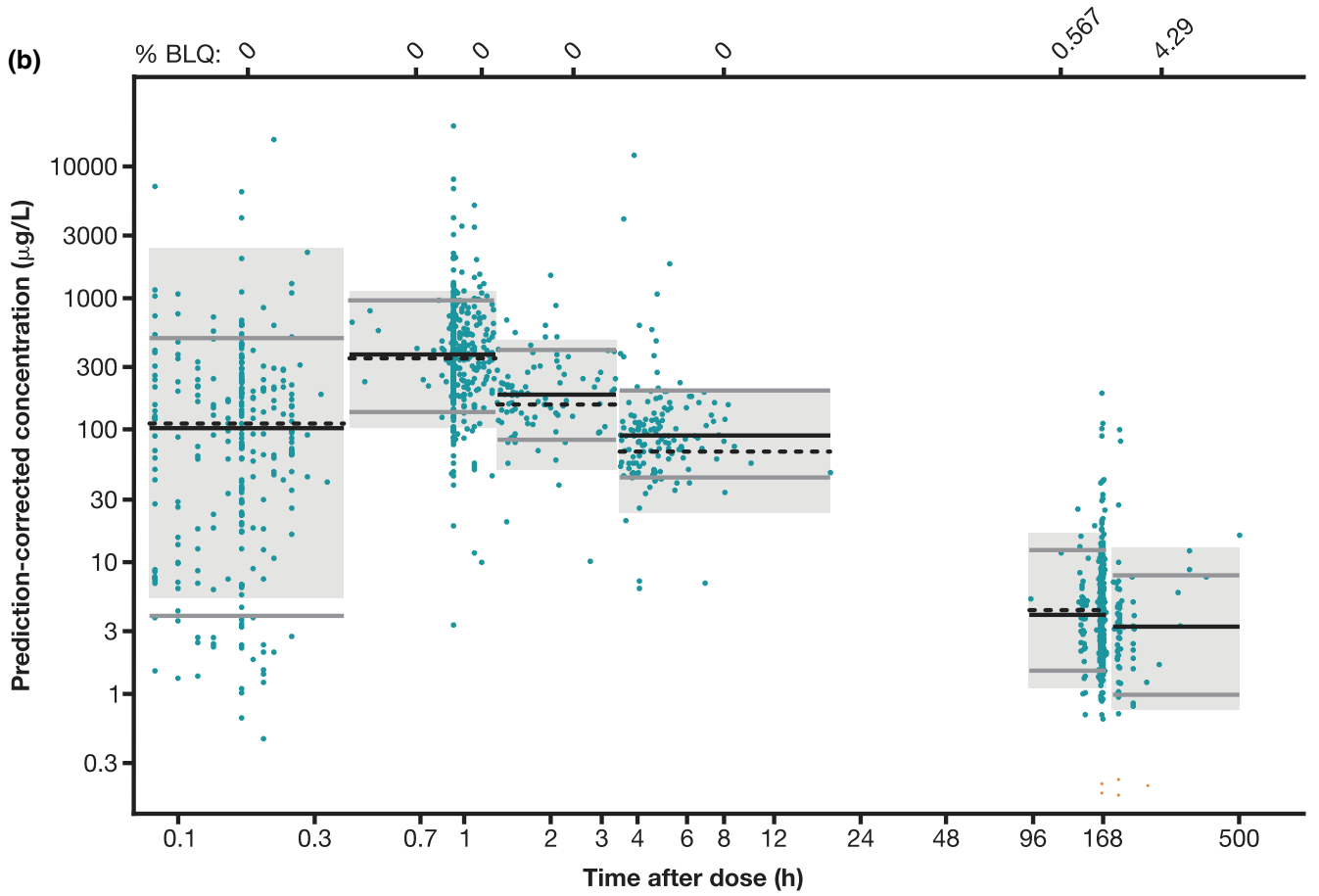


FIGURE 1 Continued

exposure and TEAEs of grade 3 or worse (Figure 5c). In the multivariate CPH analysis for time to TEAE of grade 3 or worse, final covariates in the RBCM included residence in China, residence in Japan, glycated hemoglobin, and treatment arm. Testing of the copanlisib exposure variables on the RBCM for copanlisib-treated patients showed no significant ER response for the copanlisib exposure variables $AUC_{(0-168)nd}$ ($p = 0.051$), $C_{avg,2wk}$ ($p = 0.197$), $C_{avg,4wk}$ ($p = 0.885$), and $C_{avg,8wk}$ ($p = 0.213$; Figure 5d).

Additionally, no exposure–safety relationship was identified related to the frequency of all other investigated safety events in CHRONOS-3, including hyperglycemia, hypertension, diarrhea, nausea, fatigue, lung infections, and neutropenia of any grade (Figure S3). Finally, a graphical assessment of copanlisib RDI as a function of copanlisib exposure revealed no clear relationship following administration of the copanlisib 60 mg intermittent dosing regimen (Figure S4).

DISCUSSION

This analysis provides the first comprehensive assessment of copanlisib PopPK and ER relationships from a large dataset of experience with copanlisib. Regulatory authorities have recently highlighted the importance of selecting and justifying appropriate dosing regimens for new molecular entities within proposed treatment regimens, particularly for agents deemed to have a narrow therapeutic window (including copanlisib and other PI3K inhibitors in hematologic malignancies).[29,30] Thus, there remains a need to better understand sources of between-patient variability in copanlisib PK and to evaluate whether the approved copanlisib dosing regimen is appropriate when used in combination with rituximab in the relapsed iNHL population. We established a comprehensive PopPK model for copanlisib to identify and quantify sources of PK variability from phase I–III clinical trial data. In addition, we investigated the relationship between copanlisib exposure and efficacy (PFS and ORR) and relevant safety events using data from the first large, pivotal phase III study of copanlisib with rituximab in iNHL, CHRONOS-3. The CHRONOS-3 study design (e.g., crossover following progression) and limited number of events at the 1-year follow-up precluded a direct ER analysis of overall survival.

Copanlisib PK with 60 mg flat dosing administered 3 weeks on/1 week off were well described by the comprehensive and robust PopPK model and follow three-compartment kinetics with first-order elimination from the

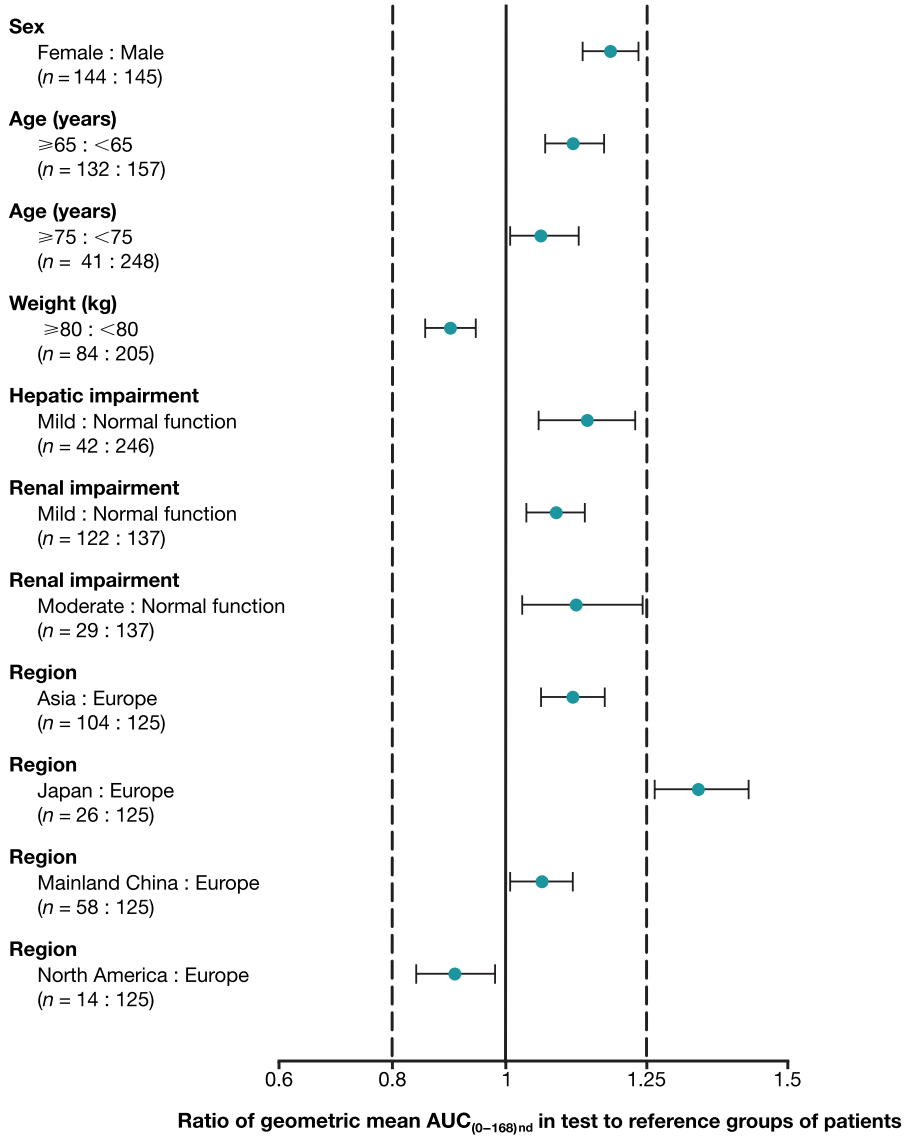
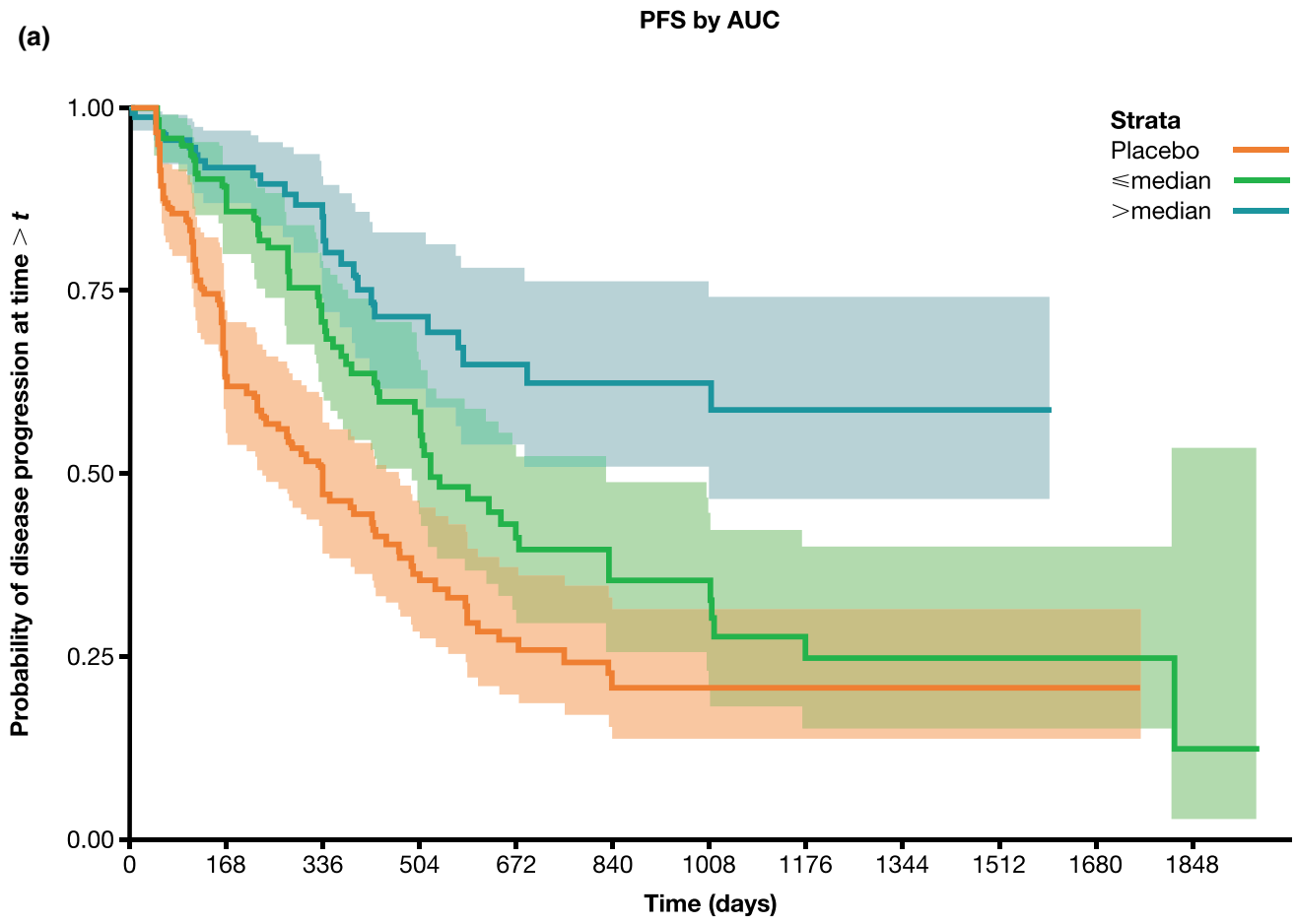


FIGURE 2 Forest plot of population pharmacokinetics-predicted copanlisib exposure ($AUC_{[0–168]nd}$) in CHRONOS-3 stratified by covariates of interest. The horizontal error bars indicate the 90% confidence intervals of the ratio of geometric means of copanlisib $AUC_{(0–168)nd}$, split by dichotomized covariates. The 90% confidence intervals were created by resampling individual steady-state $AUC_{(0–12)}$ values with replacement 1000 times from each patient subgroup. The vertical lines show the position of identity and ratios of 0.8 and 1.25. The simulations used the individual exposures at 60 mg dosing derived from the selected population pharmacokinetics covariate model. Only patients from CHRONOS-3 were included in the analysis. The forest plot excludes the display of the effect of moderate or severe hepatic impairment and the effects of drug–drug interactions with strong CYP3A inhibitors/inducers due to low patient numbers. AUC, area under the curve; $AUC_{(0–168)nd}$, nominal $AUC_{(0–168)}$. This figure was previously presented in a poster at the Third AACR International Meeting, Advances in Malignant Lymphoma: Maximizing the Basic-Translational Interface for Clinical Application, June 23–26, 2022, Boston, MA, USA, and is reproduced with kind permission from Peter Morcos on behalf of all authors.

central compartment. In the final model, eight covariates were found to statistically influence copanlisib PK. As expected, the direction of influence for co-administration of rifampin (a strong CYP3A inducer) or itraconazole (a strong CYP3A inhibitor) and hepatic function status was consistent with dedicated clinical pharmacology study results and known disposition properties for copanlisib.[17,20] A forest plot quantifying the influence of identified covariates and relevant patient subgroups demonstrated that most subpopulations fall within traditional bioequivalence boundaries, and no subpopulations showed PK differences of greater than 35%. The overall PK variability (i.e., the fifth and 95th percentiles of $AUC_{[0–168]nd}$ in CHRONOS-3 were 2647 and 5766 ng*h/mL) was greater than any differences seen in any subpopulation. The identified reduction in V1 and CL for female patients and reduction in



Number at risk

Placebo	145	82	57	35	21	13	10	5	3	2	1	0
≤median	151	100	62	40	25	17	14	9	6	4	3	1
>median	151	90	54	35	27	23	17	9	5	2	0	0

FIGURE 3 Exposure–PFS analysis in CHRONOS-3. (a) Kaplan–Meier curve of PFS stratified by treatment arm and median copanlisib exposure, and (b) forest plot of covariates and exposure metrics for PFS. (a) Kaplan–Meier survival curve with 95% CIs and risk table for PFS in all patients stratified by placebo (orange), copanlisib plasma exposure as $AUC_{(0–168)nd}$ at or below the median (green), and $AUC_{(0–168)nd}$ above the median (blue). (b) The forest plot is split into two sections, with the *x*-axis displaying the HR relative to the reference category. The top section (above the horizontal dotted line) shows the result of an initial covariate search for PFS in all patients. Categorical covariates are shown on the far left, with categories and corresponding prevalence (in parentheses) given below each category. HRs and their 95% CIs are shown numerically and visually (orange closed circles and black lines). The latter category shown for each covariate is the reference. The vertical dotted line is placed at the point estimate of the HR for copanlisib versus placebo treatment. The bottom section (below the horizontal dotted line) shows the result of testing copanlisib exposure variables on the reduced baseline covariate model for PFS in copanlisib-treated patients only. Exposure variables are shown on the far left, with the median given immediately below and the fifth and 95th percentiles shown in parentheses. HRs and their 95% CIs are shown numerically and visually (green closed circles for the fifth percentile, blue closed circles for the 95th percentile, and black lines). HRs are adjusted to be relative to placebo for all copanlisib exposure variables shown. AUC, area under the curve; $AUC_{(0–168)nd}$, nominal $AUC_{(0–168)}$; $C_{avg,2wk}$, copanlisib average past 2 weeks; $C_{avg,4wk}$, copanlisib average past 4 weeks; $C_{avg,8wk}$, copanlisib average past 8 weeks; CI, confidence interval; HR, hazard ratio; PFS, progression-free survival. This figure was previously presented in a poster at the Third AACR International Meeting, Advances in Malignant Lymphoma: Maximizing the Basic-Translational Interface for Clinical Application, June 23–26, 2022, Boston, MA, USA, and is reproduced with kind permission from Peter Morcos on behalf of all authors.

CL for patients from Japan aligned with what could be expected due to general differences in body weight. The covariates appearing in the final model provide the best description of copanlisib PK variability but do not necessarily identify the underlying driver of identified relationships. Interestingly, patients in CHRONOS-3 were

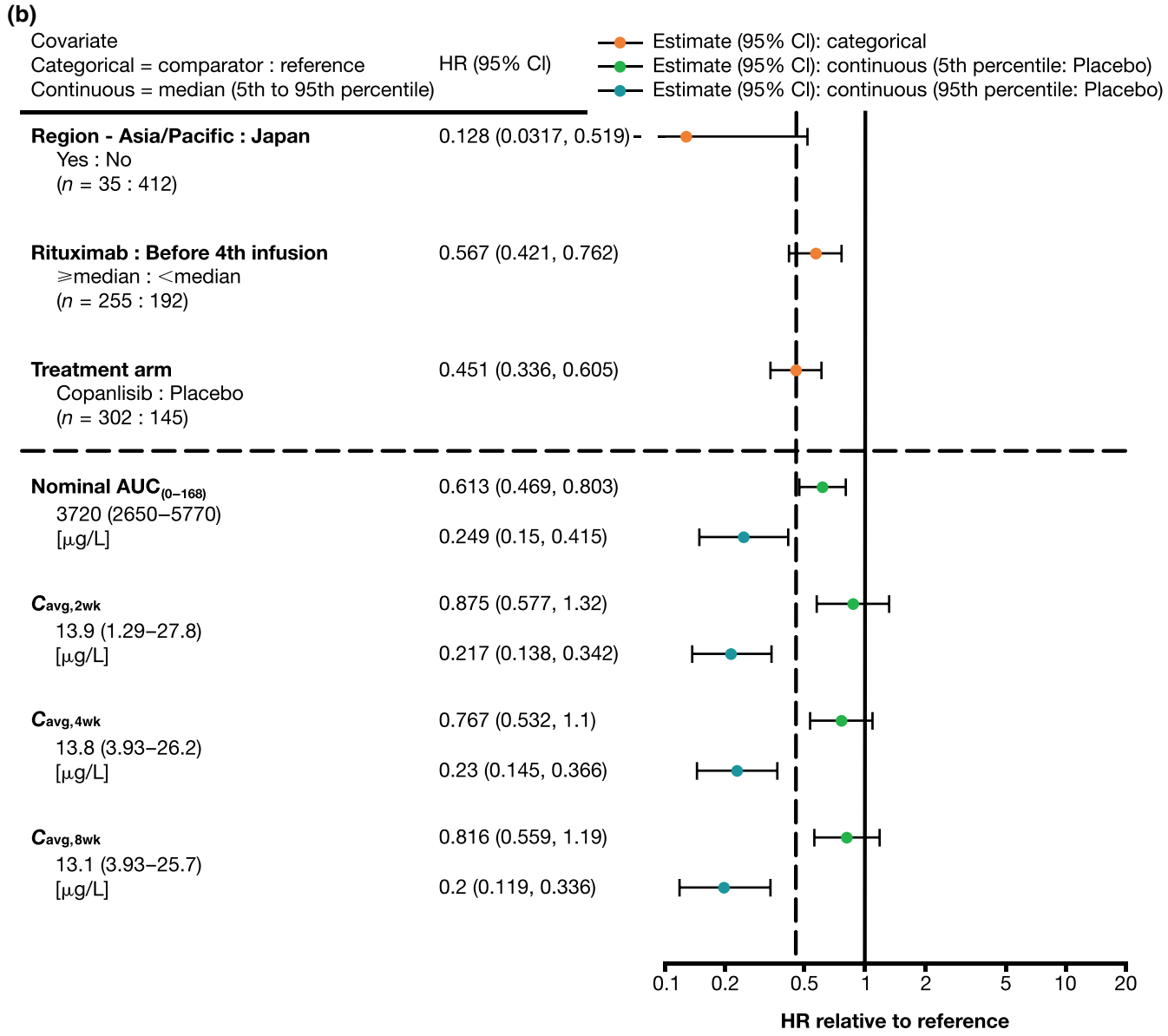


FIGURE 3 Continued

shown to have an 18.4% lower CL; however, this could not be robustly assigned to co-administration with rituximab due to differences in study design and patient population compared with the other studies. Finally, high variance was noted during model development in concentrations collected at the early stages of infusion. This was expected due to rapidly changing concentrations from the ongoing infusion and was accommodated during model development through the use of a residual error model with stratifications related to infusion time (for the first 20 min of the infusion and thereafter). Overall, the PopPK meta-analysis well characterized copanlisib PK and enabled derivation of reliable individual copanlisib exposure metrics, including time-varying metrics which account for individual dosing history, to robustly investigate ER relationships.

Treatment with copanlisib plus rituximab was associated with prolonged PFS when compared with placebo plus rituximab in CHRONOS-3.[11,31] The multivariate CPH analysis confirmed this treatment effect, and testing of copanlisib exposure variables revealed a statistically significant, positive ER relationship between higher copanlisib exposure and prolonged PFS. Thus, greater copanlisib exposures following the investigated dosing regimen are associated with prolonged PFS, supporting the selection of the MTD in this patient population and treatment setting to maximize copanlisib efficacy, whereas lower copanlisib doses may result in reduced efficacy. This positive exposure–PFS relationship was observed in addition to identified covariate effects, including geographic region and rituximab exposure (i.e., patients from Japan and patients with rituximab exposure greater

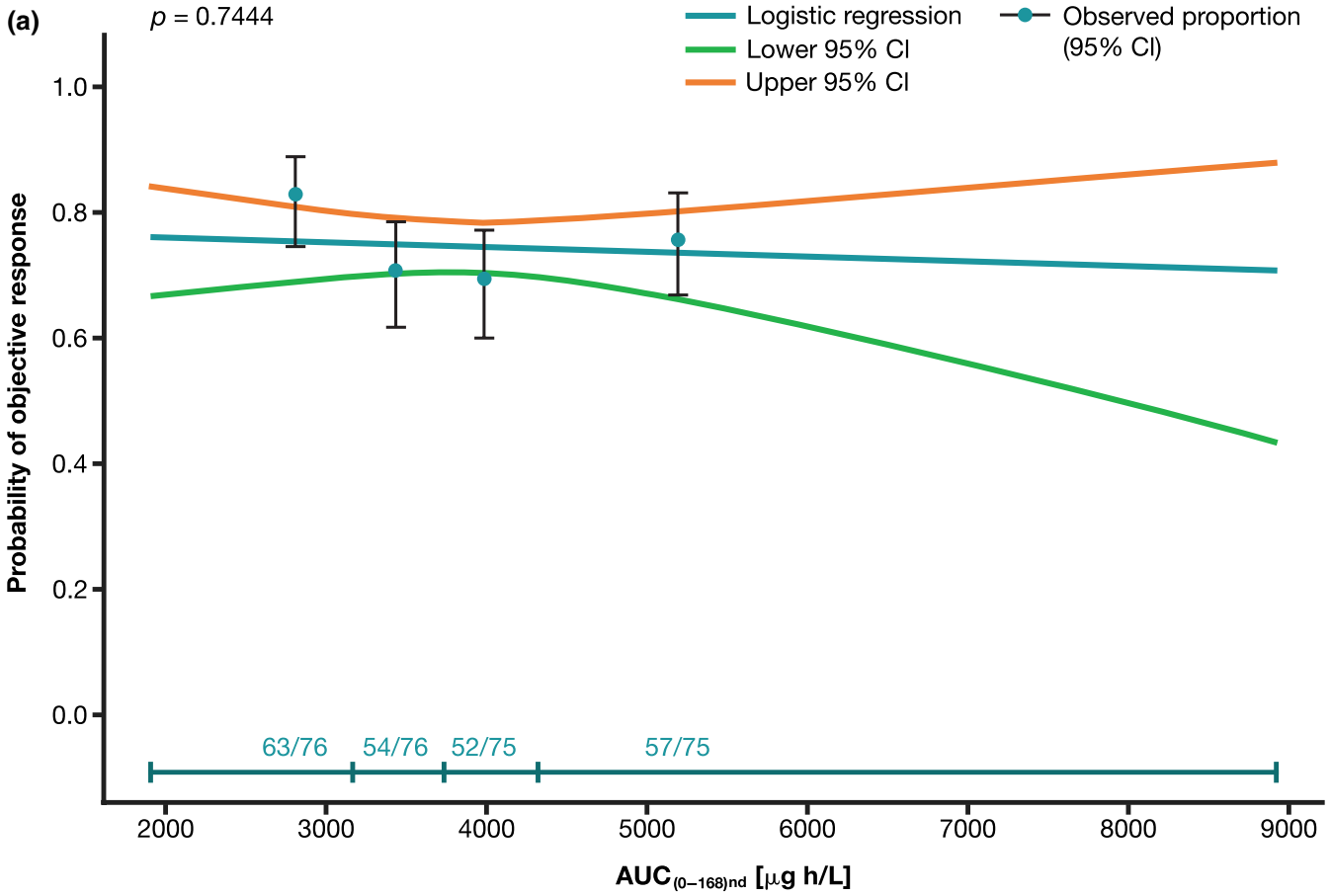


FIGURE 4 Exposure–ORR analyses in CHRONOS-3. (a) Univariate logistic regression of copanlisib $AUC_{(0–168)nd}$ versus ORR and (b) forest plot of covariates and exposure metrics from multivariate logistic regression for ORR. (a) Copanlisib $AUC_{(0–168)nd}$ is shown on the *x*-axis. Probability of objective response is shown on the *y*-axis. The solid lines represent the logistic regression fit with 95% CI. The blue points and vertical lines give the observed incidence rates and 95% CIs for each of the four quartiles of $AUC_{(0–168)nd}$ and are located at the mean value for each quartile. Observed incidences for each quartile of $AUC_{(0–168)nd}$ are given at the top of the plot. (b) The forest plot is split into two sections, with the *x*-axis displaying the odds ratio relative to the reference category. The top section (above the horizontal dotted line) shows the result of an initial covariate search for ORR in all patients. Categorical covariates are shown on the far left, with categories and corresponding prevalence (in parentheses) given below each category. Odds ratios and their 95% CIs are shown numerically and visually (orange closed circles and black lines). The latter category shown for each covariate is the reference. The vertical dotted line is placed at the point estimate of the odds ratio for copanlisib versus placebo treatment. The bottom section (below the horizontal dotted line) shows the result of testing copanlisib exposure variables on the reduced baseline covariate model for ORR in copanlisib-treated patients only. Exposure variables are shown on the far left, with the median given immediately below and the fifth and 95th percentiles shown in parentheses. Odds ratios and their 95% CIs are shown numerically and visually (green closed circle for the fifth percentile, blue closed circle for the 95th percentile, and black lines). Odds ratios are adjusted to be relative to placebo for all copanlisib exposure variables shown. AUC, area under the curve; $AUC_{(0–168)nd}$, nominal $AUC_{(0–168)}$; CI, confidence interval; FL, follicular lymphoma; ORR, objective response rate. Panel (b) was previously presented in a poster at the Third AACR International Meeting, Advances in Malignant Lymphoma: Maximizing the Basic-Translational Interface for Clinical Application, June 23–26, 2022, Boston, MA, USA, and is reproduced with kind permission from Peter Morcos on behalf of all authors.

than or equal to median PK values demonstrated prolonged PFS). The methodology applied in this analysis indicated that copanlisib exposure was significant even under the conservative assumption that prolonged PFS in patients from Japan is purely a geographic effect and unrelated to their modestly higher copanlisib exposure. Notably, incorporating copanlisib exposure first in the backward elimination covariate procedure strengthened the ER relationship further and eliminated the other covariates. Thus, this conservative approach suggests the true ER effect for PFS may be stronger than what is reported here. The exposure–ORR analyses confirmed the copanlisib benefit that was consistent throughout the copanlisib exposure range, further supporting the investigated dosing regimen in this setting.

Although results from CHRONOS-3 indicated a higher incidence of reported safety events for patients treated with copanlisib versus placebo, exposure–safety analyses

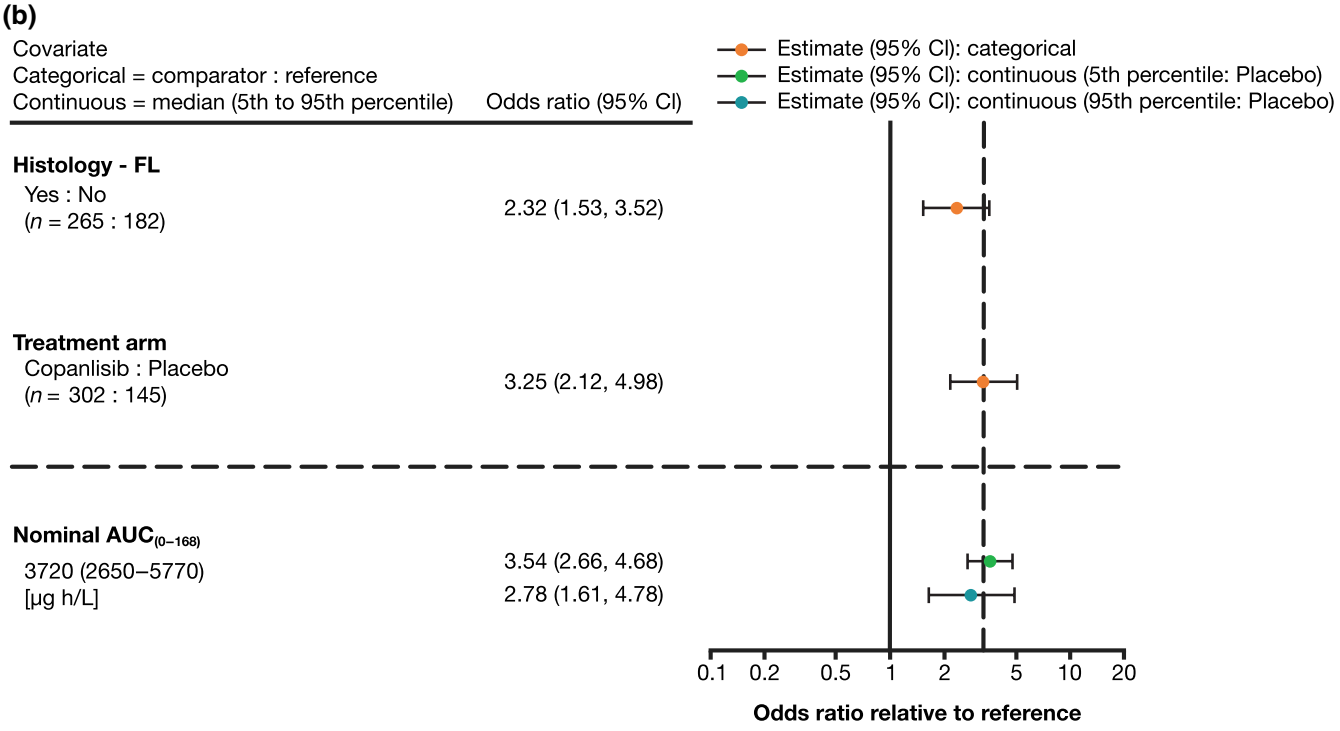


FIGURE 4 Continued

demonstrated that, beyond copanlisib treatment, no significant exposure–safety relationships were identified with the copanlisib 60 mg intermittent dosing schedule. Indeed, no relationships between exposure and SAEs or between exposure and TEAEs of grade 3 or worse were observed with regard to both the frequency of the safety event (by univariate logistic regression) and the time to safety event (by multivariate CPH analysis). Similarly, no change in the frequency of all other investigated safety events was observed for CHRONOS-3. Of note, a non-significant trend for exposure–safety relationship was reported for copanlisib in the phase II CHRONOS-1 monotherapy trial at the primary data cutoff.[32] The current analysis provides further elucidation of exposure–safety relationships in the larger phase III CHRONOS-3 trial, supporting no significant relationships. Thus, lower starting doses of copanlisib are not expected to improve safety based on analyses from this single-dose range in this patient population and combination setting. The lack of clear exposure relationship seen for copanlisib RDI (Figure S4) supports a generally consistent delivery of copanlisib 60 mg with an intermittent dosing regimen across the exposure range.

The ER relationships for copanlisib from this comprehensive analysis differ from those reported for other PI3K inhibitors. Indeed, for the majority of PI3K inhibitors, there appear to be positive exposure–safety but no exposure–efficacy relationships, suggesting inadequate dose optimization for this drug class and that lower PI3K inhibitor doses may improve tolerability without negatively affecting efficacy.[32] Differences between the ER relationships reported in this and other analyses may be due to differences in the derivation of the MTD for the individual programs or potentially to differences in treatment regimens (single agent or combinations) or dosing schedule. Unlike other PI3K inhibitors that are administered on a continuous schedule, copanlisib is dosed using an intermittent schedule. This was historically supported by preclinical experiments suggesting that transient target engagement could achieve efficacy while providing an opportunity for normal tissue recovery.[3,4] These postulations have been recently corroborated by reports suggesting that intermittent dosing of PI3K-δ inhibitors can uncouple antitumor effects from immune-related adverse events secondary to systemic effects on regulatory T cells.[33] In addition, simulations from a mechanistic quantitative systems pharmacology model of the PI3K inhibitor class have suggested that, due to the infrequent dosing of the copanlisib regimen, the inhibition of PI3K isoforms responsible for immune-mediated colitis is not sustained enough to drive progression to colitis.[34] Clinically, a phase Ib study of zandelisib, a PI3K inhibitor in development, recently reported lower treatment-related SAEs for patients receiving an intermittent dosing schedule when compared with a continuous schedule.[35] Overall, these independent investigations and the results from these PopPK and ER analyses provide support for the copanlisib intermittent dosing schedule.

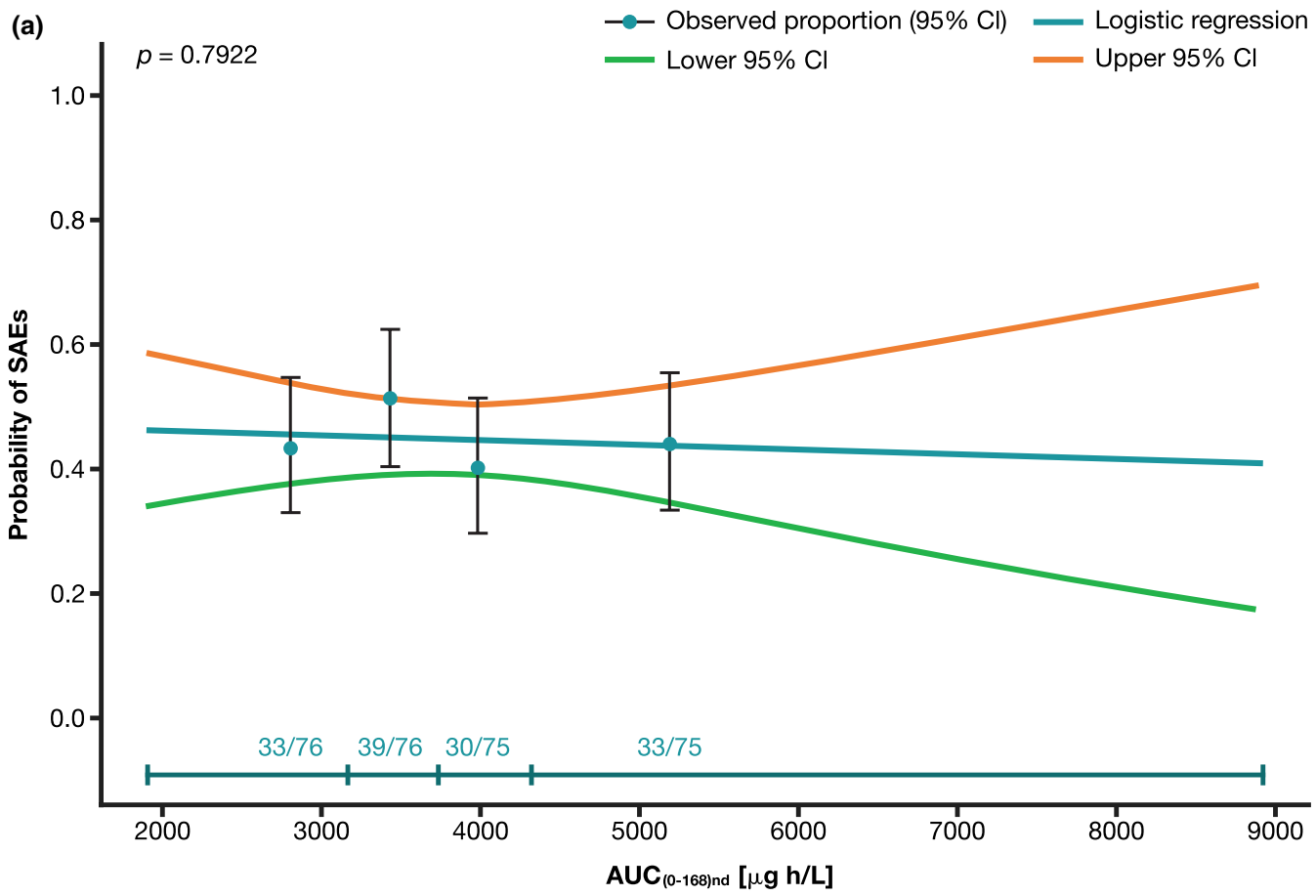
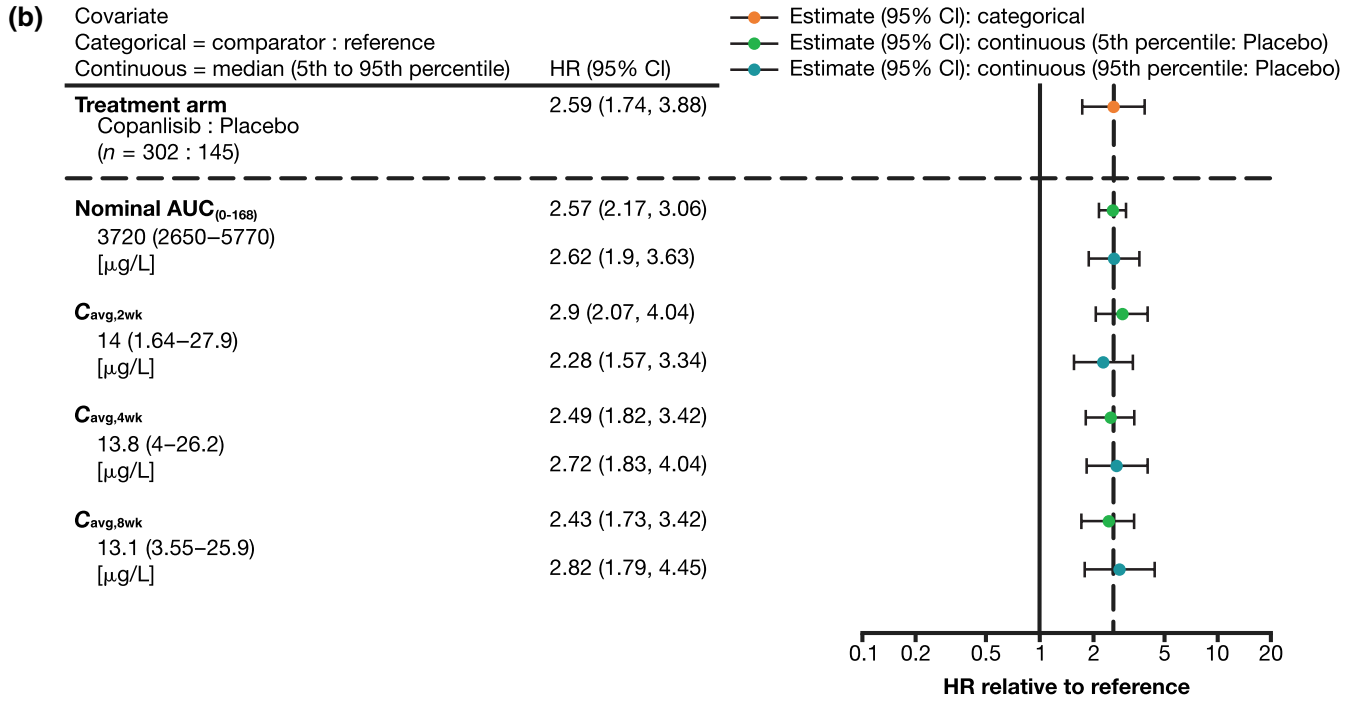


FIGURE 5 Exposure–safety analyses from CHRONOS-3. (a) Univariate logistic regression analysis for copanlisib exposure and SAEs, (b) forest plot of covariates and exposure metrics from Cox proportional hazards for time to SAE, (c) univariate logistic regression analysis for copanlisib exposure and TEAEs of grade 3 or worse, and (d) forest plot of covariates and exposure metrics from Cox proportional hazards analysis for time to TEAE of grade 3 or worse. In panels (a) and (c), the solid lines represent the logistic regression fit with 95% CI. The blue points and vertical lines give the observed incidence rates and 95% CIs for each of the four quartiles of $AUC_{(0–168)nd}$ and are located at the mean value for each quartile. Observed incidences for each quartile of $AUC_{(0–168)nd}$ are given at the top of the plot. In panels (b) and (d), the forest plot is split into two sections, with the *x*-axis displaying the HR relative to the reference category. The top section (above the horizontal dotted line) shows the result of an initial covariate search for (panel [b]) SAEs in all patients or (panel [d]) hyperglycemia (any grade) in all patients. Categorical covariates are shown on the far left, with categories and corresponding prevalence (in parentheses) given below each category. HRs and their 95% CIs are shown numerically and visually (orange closed circles and black lines). The latter category shown for each covariate is the reference. The vertical dotted line is placed at the point estimate of the HR for copanlisib versus placebo treatment. The bottom section (below the horizontal dotted line) shows the result of testing copanlisib exposure variables on the reduced baseline covariate model for (panel [b]) SAEs in copanlisib-treated patients only or for (panel [d]) TEAEs of grade 3 or worse in copanlisib-treated patients only. Exposure variables are shown on the far left, with the median given immediately below and the fifth and 95th percentiles shown in parentheses. HRs and their 95% CIs are shown numerically and visually (green closed circles for the fifth percentile, blue closed circles for the 95th percentile, and black lines). HRs are adjusted to be relative to placebo for all copanlisib exposure variables shown. AUC, area under the curve; $AUC_{(0–168)nd}$, nominal $AUC_{(0–168)}$; $C_{avg,2wk}$, copanlisib average past 2 weeks; $C_{avg,4wk}$, copanlisib average past 4 weeks; $C_{avg,8wk}$, copanlisib average past 8 weeks; CI, confidence interval; HbA_{1c}, glycated hemoglobin; HR, hazard ratio; SAE, serious adverse event; TEAE, treatment-emergent adverse event. This figure was previously presented in a poster at the Third AACR International Meeting, Advances in Malignant Lymphoma: Maximizing the Basic-Translational Interface for Clinical Application, June 23–26, 2022, Boston, MA, USA, and is reproduced with kind permission from Peter Morcos on behalf of all authors.

In summary, copanlisib PK were characterized and their covariates were elucidated using data across phase I–III studies. For CHRONOS-3, ER analyses revealed a significant exposure–PFS relationship and no significant exposure–safety relationships for investigated safety events, in the presence of potentially confounding baseline factors. These results support the clinical findings in CHRONOS-3, in which copanlisib treatment was associated with clinically meaningful benefit (PFS and ORR) while resulting in an acceptable safety profile.[11,21]



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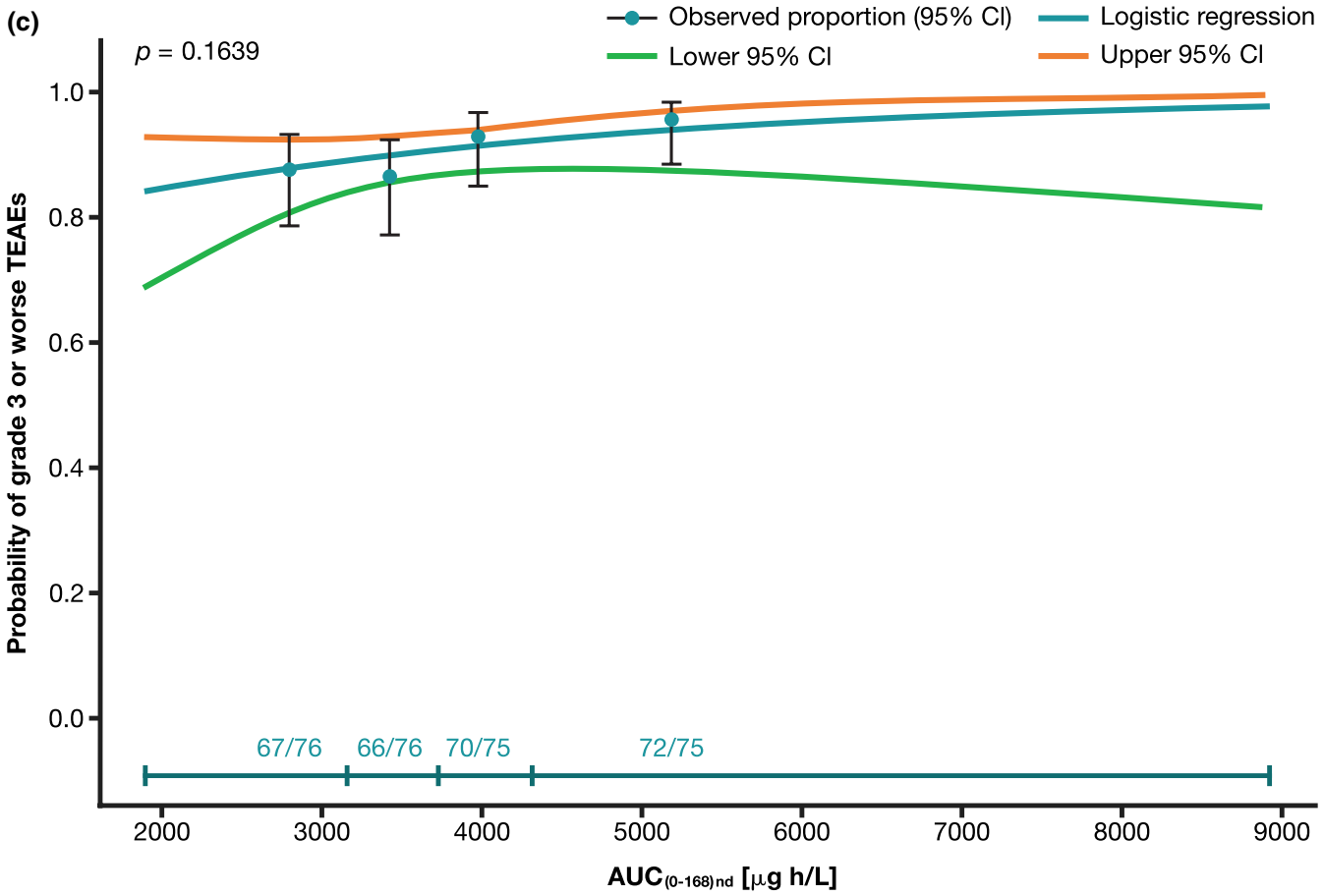

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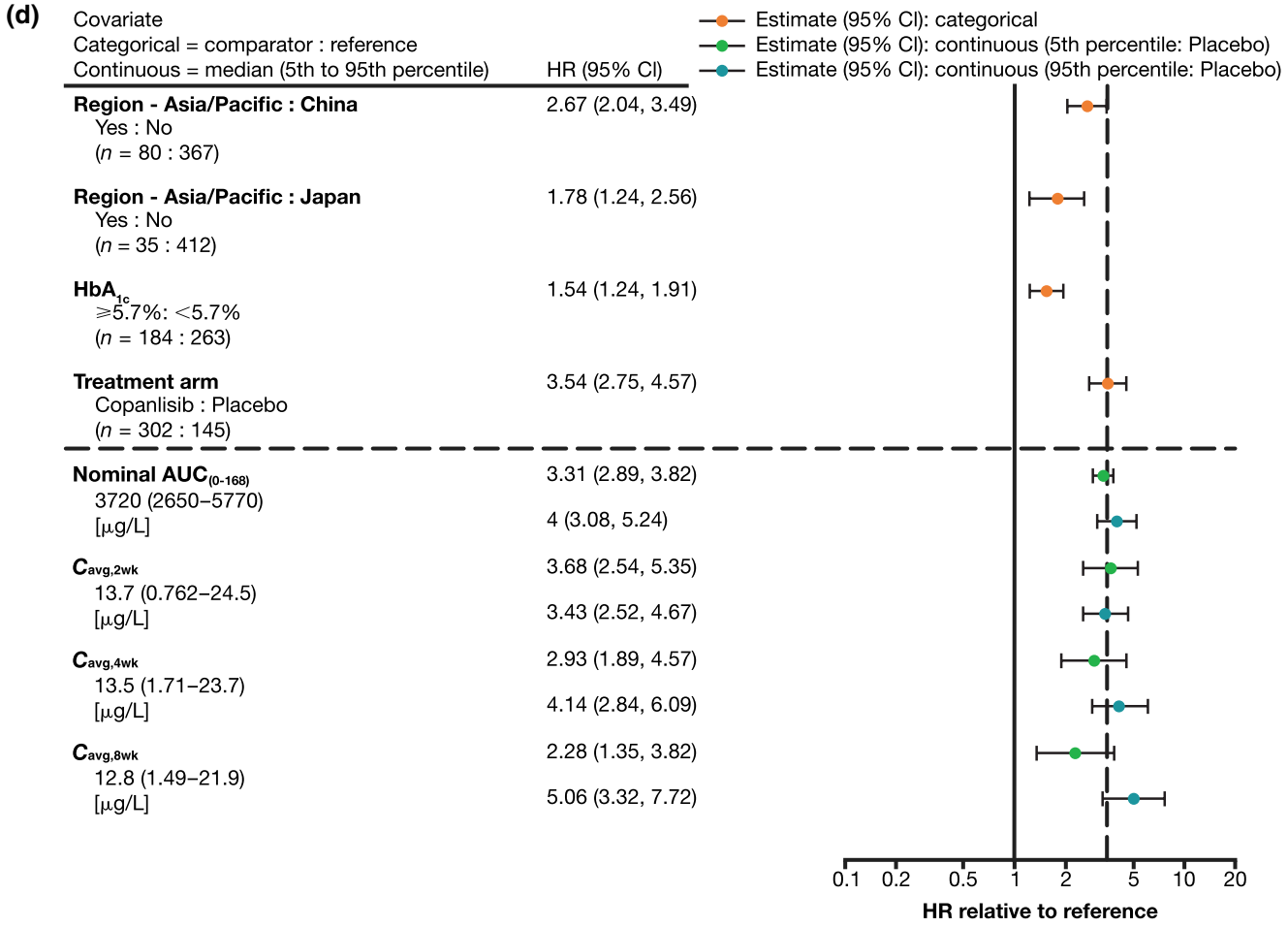

FIGURE 5 Continued

The positive exposure–PFS relationship in CHRONOS-3 and lack of significant exposure–safety relationships identified in this analysis suggest that starting with lower copanlisib doses may result in reduced efficacy but may not necessarily result in improved safety when used in combination with rituximab in patients with relapsed iNHL. It should be noted, however, that the ER analyses are based on data collected from CHRONOS-3 which evaluated only one copanlisib dosing regimen. Thus, inferences on the ER relationship are confined within the exposure range achieved with the investigated copanlisib dosing regimen. Nonetheless, the derivation of the time-varying exposure metrics, which accounted for dosing history (including dose modifications), enabled a dynamic exposure range to support robust evaluation of ER relationships. As ER relationships may differ across patient populations and treatment settings, additional ER analyses are ongoing and planned for copanlisib when used in monotherapy in patients with relapsed or refractory indolent B-cell lymphoma who had previously received at least two therapies in CHRONOS-1 based on long-term follow-up and when used in combination with rituximab and chemotherapy in patients with relapsed iNHL in the ongoing second phase III study, CHRONOS-4. Overall, the outcomes from the CHRONOS-3 ER analyses substantiate the current dose selection of copanlisib 60 mg administered on days 1, 8, and 15 of a 28-day cycle, along with the reported clinical efficacy and safety results of copanlisib when used in combination with rituximab in iNHL.

AUTHOR CONTRIBUTIONS

All authors wrote the manuscript. F.H., P.L.Z., L.M.S., and B.H.C. designed the research. All authors performed the research and all authors analyzed the data.

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CONFLICT OF INTEREST STATEMENT

P.N.M., L.M.S., and B.H.C. are employees of Bayer HealthCare Pharmaceuticals, Inc. and may hold stock or stock options. J.M. and R.A. are employees of BAST Inc. Limited and may hold stock or stock options. F.H., V.B., and D.G. are employees of Bayer AG and may hold stock or stock options. P.L.Z. has acted as a consultant for EUSA Pharma, MSD, and Novartis, participated in speaker bureaus for Beigene, BMS, Celltrion, EUSA Pharma, Gilead, Incyte, Janssen-Cilag, Kyowa Kirin, MSD, Novartis, Roche, Servier, Takeda, and TG Therapeutics, and participated in advisory boards for ADC Therapeutics, Beigene, BMS, Celltrion, EUSA Pharma, Gilead, Incyte, Janssen-Cilag, Kyowa Kirin, MSD, Novartis, Roche, Sandoz, Secura Bio, Servier, Takeda, and TG Therapeutics.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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